Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: a single-blinded randomized controlled trial

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Abstract: BACKGROUND AND PURPOSE: This randomized controlled trial tests the efficacy of bilateral arm training with rhythmic auditory cueing (BATRAC) versus dose-matched therapeutic exercises (DMTEs) on upper-extremity (UE) function in stroke survivors and uses functional magnetic resonance imaging (fMRI) to examine effects on cortical reorganization. METHODS: A total of 111 adults with chronic UE paresis were randomized to 6 weeks (3×/week) of BATRAC or DMTE. Primary end points of UE assessments of Fugl-Meyer UE Test (FM) and modified Wolf Motor Function Test Time (WT) were performed 6 weeks prior to and at baseline, after training, and 4 months later. Pretraining and posttraining, fMRI for UE movement was evaluated in 17 BATRAC and 21 DMTE participants. RESULTS: The improvements in UE function (BATRAC: FM Δ = 1.1 + 0.5, P = .03; WT Δ = -2.6 + 0.8, P < .00; DMTE: FM Δ = 1.9 + 0.4, P < .00; WT Δ = -1.6 + 0.7; P = .04) were comparable between groups and retained after 4 months. Satisfaction was higher after BATRAC than DMTE (P = .003). BATRAC led to significantly higher increase in activation in ipsilesional precentral, anterior cingulate and postcentral gyri, and supplementary motor area and contralesional superior frontal gyrus (P < .05). Activation change in the latter was correlated with improvement in the WMFT (P = .01). CONCLUSIONS: BATRAC is not superior to DMTE, but both rehabilitation programs durably improve motor function for individuals with chronic UE hemiparesis and with varied deficit severity. Adaptations in brain activation are greater after BATRAC than DMTE, suggesting that given similar benefits to motor function, these therapies operate through different mechanisms.

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Title Page

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Abstract

Background and Purpose. This randomized controlled trial tests the efficacy of bilateral arm training with rhythmic auditory cueing (BATRAC) vs. dose-matched therapeutic exercises (DMTE) on upper extremity (UE) function in disabled stroke survivors and uses functional magnetic resonance imaging (fMRI) to examine the effects on cortical reorganization.

Methods. One hundred eleven adults with chronic UE paresis were randomized to 6 weeks (3x/week) of BATRAC or DMTE. Primary endpoints were the UE. Assessments of Fugl-Meyer UE Test (FM) and modified Wolf Motor Function Test Time (WT) were performed 6 weeks prior to and at baseline, after training, and 4 months later. Pre and post training, fMRIon UE movement was evaluated in 17 BATRAC and 21 DMTE subjects.

Results. The improvements in UE function (BATRAC: FM $\Delta = 1.1 \pm 0.5$; $p = 0.03$; WT $\Delta = -2.6 \pm 0.8$; $p < .00$; DMTE: FM $\Delta = 1.9 \pm 0.4$; $p < .00$; WT $\Delta = -1.6 \pm 0.7$; $p = .04$) were comparable between groups, and retained after 4 months. Satisfaction was higher after BATRAC than DMTE ($p=0.003$). BATRAC lead to significantly higher activation increase in ipsilesional precentral, anterior cingulate and postcentral gyri, SMA and contralesional superior frontal gyrus ($p<0.05$). Activation change in the latter was correlated with improvement in the WMFT ($p=0.01$).

Conclusions. BATRAC is not superior to DMTE but both rehabilitation programs durably improve motor function for individuals with chronic UE hemiparesis and with varied deficit severity. Adaptations in brain activation are greater after BATRAC then DMTE suggesting that, given similar benefits to motor function, both therapies operate through different mechanisms.

Introduction

Rehabilitation for stroke survivors with moderate to severe limitations of the paretic arm after stroke remains a challenge. Furthermore, there are few randomized controlled trials testing unilateral or bilateral upper extremity (UE) rehabilitation interventions [1-5]. The largest recent trial demonstrated that two weeks of Constraint Induced Movement Therapy (CIMT) significantly improves UE function more than usual care, persisting for at least 24 months [6, 7]. However, CIMT requires ability to partially extend the wrist and fingers that limits the success of CIMT in many stroke survivors. In contrast, bilateral UE training with rhythmic auditory cueing (BATRAC) is targeted to rehabilitate stroke survivors with greater UE impairments than CIMT.

BATRAC, like CIMT, is based on motor learning principles, including repetition, feedback and goal-setting. Thus, it is similar to CIMT in overcoming learned non-use and relative inactivity, [6, 8-14] but it also includes use of the non-paretic arm as a fundamental component of the training based on interlimb coupling theory, where the two arms act to form a "neurofunctional" unit [15-17]. Evidence from studies of non-disabled suggest that bilateral arm movements engage additional brain circuits, for example in the supplementary motor area and primary motor cortex [18-20 21, 22]over and above the combination of similar unilateral arm movements. Thus, training these circuits is useful for bilateral movements and there also appears to be a neurophysiologal and functional transfer effect to unilateral movements after short-term training in non-disabled [23] as well as those with stroke [24]. Plausible pathways that are disinhibited or facilitated during bilateral as oppose to unilateral movements include transcallosal [25], ipsilateral uncrossed cortico-spinal and bilateral brainstem pathways such as rubrospinal or propriospinal [26]. Taken together, the neurophysiological and functional evidence suggest a possible benefit from bilateral arm training to the paretic arm.

Uncontrolled studies of BATRAC [27-29] show functional benefits, and one small controlled study showed increased bi-hemispheric cortical activation associated with improved UE function after BATRAC, suggesting cortical plasticity

[30]. The small sample, heterogeneity of the functional and MRI responses, and no assessment of durability led to this randomized controlled trial to test the hypotheses that BATRAC will result in larger and more durable UE functional gains mediated through remodeling of bihemispheric motor and/or pre-motor cortical networks compared to dose-matched unilateral therapeutic exercises (DMTE controls).

Material and Methods

Recruitment, screening, enrollment and randomization of participants was at the Baltimore Veterans Affairs Medical Center (VAMC) and involved referrals from University of Maryland (UM) Medical System Hospital and region-wide advertisements (Figure 1). Those included had a unilateral stroke >6-months prior, could follow simple instructions, had volitional control of the nonparetic arm and the ability to flex the paretic arm shoulder three inches from a neutral position. Exclusion criteria included symptomatic heart disease, uncontrolled hypertension (>180/100), significant orthopedic or chronic pain conditions, untreated post-stroke depression (Center for Epidemiological Studies Depression Scale; cut-off > 16), active cancer, severe obstructive pulmonary disease, cognitive loss measured using the Folstein mini mental state examination (< 22 points), aphasia with inability to follow two-step commands. All were screened for the fMRI sub-study and excluded only if they had metal implants, metal shards from injury, or claustrophobia. X additional participants had their fMRI data excluded because they were part of a preliminary study[30] and we did not want to bias results. These participants remained in the present study for functional data since this was not the focus of the previous study. The study was approved by both the Institutional Review Boards of the UM Baltimore and VAMC, and participants provided informed consent. Participants were recruited for screening between January 2002 and April 2006. After screening, 142 patients were enrolled and 111 randomized after B2 to receive BATRAC or DMTE.

Insert Figure 1 about here

Design

Functional measures were collected (1) at two baseline times (B1,2) separated by 6-weeks, (2) after 6-weeks BATRAC or DMTE intervention, and (3) 4-months after intervention. Training started after B2. After training, participants were asked to use their paretic arm in daily life, but not in new UE training regimens. FMRI data were collected at B2 and after training.

Primary Endpoints of Upper extremity assessment

(1) Motor impairment was assessed through the Fugl-Meyer (FM) UE Test which is a reliable and valid test of single joint movements, tasks and reflexes [31-33].

(2) Motor function was measured as the time (WT) required to perform 15 tasks of a reliable and valid modified version of the Wolf Motor Function Test (WMFT) [34-36].

Secondary Endpoints of Upper extremity assessment.

(3) Components of the WMFT including maximum weight carried ("Wolf weight"), grip strength ("Wolf grip") and a qualitative assessment of UE performance ("Wolf function"). The test was modified for moderately impaired participants. We removed one level of "Wolf function" ordinal scale that included use of the non-paretic arm. We have shown this modified test is reliable and valid [34]using a sub-set of the present dataset. The WT test was administered three times at B1 to establish performance stability. The result of the second test was used to measure of performance at B1; an analysis showed performance had stabilized by the 2nd administration [34].

(4) The Stroke Impact Scale, a reliable and valid questionnaire for this population [37, 38],

(5) Isokinetic strength of elbow flexion/extension movements of both arms measured on a Kincom Dynamometer (Chattanooga, Tennessee).

(6) Isometric strength of both arms measured with the Chatillon Force Dynamometer (The Scale People, Maryland) and a Baseline→ Hydraulic Hand Dynamometer (Kom Kare, New York).

(7) Range of motion measures included shoulder flexion/extension/abduction, elbow flexion/extension, wrist flexion/extension and thumb opposition, but no mean changes exceeded the recognized 5º measurement error [39]and these data are omitted.

(8) Two verbal assessments of the participant's perceptions after training were assessed using a five-point Lickert scale where "3" indicates neither satisfied nor dissatisfied with the training and neither improved nor declined after training, respectively. For both questions, a higher score is favorable.

Functional Magnetic Resonance Imaging (fMRI)

FMRI was performed using a 1.5 T scanner (Philips, Eindhoven, The Netherlands) at the Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD as previously described [30]. Briefly, 60 coronal blood oxygenation-level dependent (BOLD) weighted scans (echo planar imaging sequence, TE=40ms, TR=3sec, 35-39 slices, slice thickness 5mm) covering the entire brain were acquired first from the non-paretic and then the paretic arm. For each arm, scans were obtained during three cycles of rest (10 images) followed by arm movement (10 images) performed in response to an auditory cue given via headsets once every three seconds. During imaging, the arm was strapped to a device that allowed elbow flexion/extension in one plane within a defined range of motion from 45° relative to standard anatomical position to 60-75° depending on the participant's paretic arm movement ability. Each subject's range of motion was also applied to the nonparetic arm and subsequently kept constant. Compliance with the protocol and the presence or absence of mirror movements and head motion was assessed through a video monitor using two cameras (head and arms). A limitation of our methodology is the lack of concurrent EMG which would better detect CNS activation in the other arm. A T1-weighted image set (3D-MPRAGE, resolution 1x1x1mm^3) was acquired for anatomical localization. Data were processed using SPM5

(www.fil.ion.ucl.ac.uk/spm/software/spm5). Standard analysis protocols, including correction for slice timing differences, head motion (< 3mm in any coordinate) and normalization to the MNI coordinate space, were used. Talairach space registration was evaluated individually, the skull was removed and all cortical lesions were masked to avoid image distortion. If not satisfactory, the registration process was repeated without skull removal or with a modified lesion mask, resulting in successful registration for all participants. All image data from participants with left-sided lesions were flipped about the mid-sagittal plane, such that the affected hemisphere was always on the right. First-level statistical parametric maps were computed including both the pre-training and the post-training scans of a given subject. A contrast post - pre was employed to identify those voxels whose activation increased between time points. Brain activation was measured by computing the first eigenvariate for each series (i.e. the scan for each time point) and for each of two pre-specified (primary) regions of interest (ROI) and six additional exploratory ROIs and time point. All ROIs were selected from the Automated Anatomical Labelling (AAL) atlas [40]. Primary ROIs were pre-specified in the study protocol and were selected based on a priori knowledge of brain activation changes during BATRAC [24]. Precentral gyrus and superior frontal gyrus were primary ROIs (Figure 2). Secondary ROIs had not been pre-specified and were selected based on a review of single subject maps. Secondary ROIs included postcentral gyrus, cerebellar hemispheres (anterior and posterior lobes), supramarginal gyrus, anterior cingulate cortex and supplementary motor area. These regions were used exactly as defined in the AAL atlas (for a detailed visualization refer to http://www.cyceron.fr/web/aal__anatomical_automatic_labeling.html).

Insert Figure 2 about here

Randomization and Blinding

Participants were randomized after B2 to receive either BATRAC or DMTE using a stratified block allocation scheme based on initial function (NIH Stroke Scale with 2 as cut-off) and motor dominance of stroke. Since eligibility for fMRI analysis was not a stratification factor, the two groups were slightly unbalanced. Participants were aware of the treatment differences, but did not know that DMTE was a control intervention; thus, they reasonably expected an improvement regardless of group. Testing was conducted in a separate location from the training site by trained testers blinded to group assignment. .

Training

Training occurred 3-times per week for 6-weeks, mimicking that of an outpatient clinic, for a total of 18 sessions for each participant. There was a 9-week limit for completing the 18 sessions, as previously described [30]. For BATRAC, participants were seated at the training apparatus that consisted of T-bar handles attached to nearly frictionless linear tracks. They completed five-minutes of training with the arms moving simultaneously (in-phase) away and then towards the body in time to a metronome set at their preferred speed, followed by ten-minutes of rest. Training continued for five-minutes with the arms moving alternately (antiphase) again with auditory cuing at a preferred speed, followed by 10 minutes rest. In-phase and antiphase training blocks were repeated once each, achieving a total of 20 minutes of active continuous bilateral arm training in one hour for each participant. The frequency was held constant after the third session to allow for initial adaptation to the task. Those participants who were unable to grasp the handles independently had their hands strapped to the t-bar. If necessary, anti-gravity arm support was provided to avoid an improper arm position during the training, however, the participants were encouraged to produce the forward and backward motions actively and to reach further with their paretic arm throughout the training period by increasing the distance to the target stop. Neither frequency nor resistance was progressed.

DMTE involved a customized set of four exercises based on neurodevelopmental principles, including thoracic spine mobilization with weight shifting, scapular mobilization, weight-bearing with the paretic arm (elbow fixed), and opening the hand with finger extension. This treatment emphasizes handling techniques that facilitate body and limbs to assume "normal" positions. Participants were encouraged to actively move during the handling. DMTE was performed using the exact same time schedule as BATRAC (four cycles of active continuous five-minutes training followed by 10 minutes of rest). Thus, each participant of both groups had equal, one on one contact with trainers and equal time training but the number of movements for each participant varied according to ability. Pilot work indicated that participants needed breaks after about five minutes of active continuous training.

A treatment fidelity study was conducted in year three by personnel not affiliated with the study. Treatment fidelity was assessed with regard to design, training, delivery and receipt [41]. One design concern raised during the review was that participants were treated within the same general facility as a separate lower extremity training study. However, participants in the two arms of the present study were trained individually in a room and therefore did not observe the alternative arm training protocol. Adverse events reported were not related to the study interventions and occurred equally between the two groups.

Statistical Analysis

There were no intermediate analyses but separate data analyses for baseline, intervention, and retention phases. An intention-to-treat- analysis included all participants at each time regardless of whether they completed the study. The stability of the measures from B1 to B2 was modeled in random-effects ANOVA (SAS proc mixed, random intercept). The changes in outcome measures during BATRAC vs. DTME were compared using ANOVA adjusted for age, sex, log years since index stroke, the presence or absence of a motor dominant stroke, and the pre-intervention

B2 value of the outcome. A similar model compared changes in outcome measures between groups during retention. A Wilcoxon ranked sums test analyzed the Lickert scale data. All analyses were two-tailed with significance $p<0.05$.

Whether BATRAC and DMTE differently affected brain activation during paretic or non-paretic limb movement was analyzed using separate models for each ROI of each side of the brain (contralesional and ipsilesional). Dependent variables were the difference in the ROIs eigenvariates after therapy minus before. Independent variables included group (BATRAC vs. DMTE) and baseline brain activation (eigenvariate) for the respective ROI. Within-group correlations between change in Wolf Time and change in ROI activation were assessed using Pearson's correlation coefficients. Corrections for multiple comparisons are applied for pre-specified (4) and well as the secondary (12) ROI.

Results

A total of 119 subjects were studied during the baseline (8 dropped out between B2 and randomization). Table 1 shows the physical characteristics of the 92 who completed either BATRAC or DMTE. There were no significant differences between study groups with respect to age, gender, time since stroke, side or dominance of stroke or baseline functional scores.

Insert Table 1 about here

Endpoint Analysis

Pre-intervention. The two primary endpoints, FM and WT did not change during the 6-week baseline period. There were no differences in the secondary endpoint variables except for a decline of 0.18 on the five-point scale ($p<0.02$) for Wolf Function and 0.12 Kilograms ($p<0.02$) for paretic arm elbow flexion isometric strength.

Intervention. Data (average of B1 and B2 to post-intervention) are presented in Table 2 and include primary endpoints first followed by secondary endpoints. Both interventions improved FM scores, but there was no between group difference in improvement. The FM change ranged from +8 to -5 in BATRAC and +11 to -3 in DMTE. A significant decrease in average WT within the groups also found no significant between-group difference. The WT change ranged from -23.1 to 4.6 in BATRAC and -14.3 to 9.7 in DMTE. There was a significant increase in ability to lift a weight following BATRAC, but not DMTE (Wolf Weight); and no between-group difference. The model was significant ($r^2 = .22$) indicating that being female and having a more recent stroke predicted an improvement in this variable. There was a significant within-group improvement in movement quality (Wolf Function) following each intervention, but no between-group difference.

Following BATRAC, the sub-sections of Hand and Strength of the Stroke Impact Scale improved significantly, but there were no between-group differences. The model for Strength was significant ($r^2= .27$) indicating that a lower initial score for this sub-section is a predictor of an improved score after intervention. Following DMTE, the total score and the sub-sections Hand and Emotion demonstrated significant improvements. The model for Emotion was significant ($r^2= .30$) indicating that a lower initial score for this sub-section is a predictor of an improved score after intervention.

There was an increase in isokinetic strength in elbow extension for both arms following BATRAC, but not DMTE. BATRAC significantly improved isometric strength in non-paretic arm shoulder extension, wrist extension and wrist flexion and in paretic arm shoulder extension, while DMTE improved strength in paretic arm shoulder and wrist extension and elbow flexion. There was a greater improvement in non-paretic elbow flexion and wrist flexion isometric strength after BATRAC and in paretic wrist extension isometric strength after DMTE.

On the Lickert scale questionnaire, satisfaction with BATRAC was significantly higher than with DMTE immediately after training (4.4 vs. 3.8, p = 0.003) and remained slightly higher after the retention period (4.1 vs. 3.8, p=NS). Both groups reported comparable perceived improvements immediately after training (BATRAC 4.0 vs. DMTE 3.7) and after retention (4.1 vs. 3.9*).*

Retention During the 4-month retention there were comparable declines in FM scores by 1.1 ($p<.04$, n=39) in BATRAC and 1.0 ($p<.05$, n=39) in DMTE. The WT and secondary variables that improved after intervention were maintained during retention. However, the SIS total score response during retention differed between groups, improving by 10 after BATRAC and declining by 16 after DMTE ($p<0.05$).

fMRI Analysis In the subset of 17 BATRAC and 21 DMTE who underwent fMRI scanning, brain activation during paretic limb movement was differentially affected by the two therapies. Among the pre-specified ROIs BATRAC lead to a significantly greater increase of activation in ipsilesional precentral gyrus (contralateral to the moving, paretic limb, between group p=0.011) and contralesional superior frontal gyrus (p=0.012, Table 3). See Figure 2. These probabilities remain significant if corrected for four comparisons (2 ROIs on each side) using Bonferroni‘s correction. A statistical „trend“ ($0.05<p<0.1$) was noted for the ipsilesional superior frontal gyrus. Secondary ROIs that increased

more after BATRAC than DTME included ipsilesional SMA, anterior cingulate cortex and postcentral gyrus (Table 3). None of these between group tests remained significant after correcting for 12 comparisons (6 ROIs on each side). All other regions except the posterior lobe of the cerebellum increased more after BATRAC than DMTE, but no between group differences were significant.

Insert Figure 2 about here

The activation increase in the contralesional superior frontal gyrus predicted 38% of the improvement in WT outcomes after BATRAC ($p=0.010$; if corrected for $n=4$ comparisons, 2 primary ROIs on each side, $p=0.040$, Figure 3). Secondary ROIs whose increase in activation correlated with the improvement in WT included bilateral anterior cingulate cortex and supramarginal gyrus. These correlations except the one for the ipsilesional supramarginal gyrus remained significant after correcting for 12 comparisons (6 secondary ROIs on each side). The improvement in WT after DTME was predicted by increased activation in ipsilesional superior frontal gyrus, contralesional supramarginal gyrus and bilateral postcentral gyrus, however, none of these correlations remained significant after multiple comparison correction. No area of decreased activation was found after either BATRAC or DMTE. There were no within- or between-group treatment differences in the activation changes for either ROI or side during non-paretic limb movement.

Insert Figure 3 about here

Discussion

This randomized controlled trial demonstrates that 1) BATRAC is not superior to DMTE but both improve paretic arm function in stroke survivors, and these improvements are largely maintained for 4 months, 2) BATRAC may operate through activation of primary and secondary motor cortices while DMTE may use additional mechanisms, 3) BATRAC provides higher patient satisfaction than DMTE and 4) no co-variates consistently predicted outcome across variables. Our finding of comparable functional improvements, despite brain activation following BATRAC, disproves our hypothesis.

The improvement found in motor function after 6 weeks of BATRAC is consistent with previous studies [28-30, 42], however, DMTE produced better results than expected. Repetition or deliberate practice are major contributors to motor recovery, [43, 44] and both BATRAC and DTME involve multiple active repetitions of specific movements. Thus, in our effort to control for the repetition built into BATRAC, as well as matching the dose by time, the control group received a viable treatment program. Unlike the EXCITE trial that used a usual care control group [6] other randomized trials of UE rehabilitation that use active dose-matched training as controls also fail to show differences in outcomes between treatments [13, 45, 46]. Hence, different forms of active training are better than no training. Moreover, the within-group gains seen after six-weeks of either training program were not observed in the six-weeks between the two baseline assessments. Several other trials of UE rehabilitation also demonstrate this point using natural history/delayed entry controls [6] or attention controls receiving lower extremity [47] or non-movement exercises [12]. While the latter control nicely for general physiological effects of exercise or confounds of repeated assessments, they do not constitute an active alternative training control targeting the limb of interest comparable to DMTE. The choice of an active comparison dose-matched control design invites a degree of improvement that may not differ significantly from the experimental group in the magnitude of functional outcomes. This suggests that the specific features that differentiate BATRAC from DMTE, such as bilaterality and rhythmic cueing, may convey no additional benefit over repetition for the primary endpoints. However, progressing the intensity of either therapy has yet to be

tested, and may offer potential for greater improvement. We also are exploring whether any subject characteristics predict who will best benefit from BATRAC and/or DMTE.

There are discrete differences between BATRAC and DMTE in the pattern of improvement across secondary outcome measures. BATRAC, which requires active shoulder and elbow movements of both arms, results in specific strength gains for these two joints across both arms, while DMTE, which focuses on paretic shoulder, elbow and wrist extension, does improve these joint actions. This differential result reflects our prior finding that BATRAC improves temporal and spatial aspects of bilateral reaching, while DMTE only improves a temporal aspect of unilateral reaching [48]. It may be beneficial to combine selected components of BATRAC and DMTE in sequence or parallel in future studies. Of note is that BATRAC requires less interaction between trainer and participant because the apparatus and cueing guide the training, while DMTE requires physical support and assist to facilitate progress. Hence, BATRAC might be relatively easier to translate into self-directed training in the clinic or home. The greater sense of satisfaction and positive trend in total SIS scores during retention in the BATRAC group occurred despite the closer trainer-subject relationship with DMTE, and could have implications for compliance in community trials.

Finally, although our results suggest that both BATRAC and DMTE are viable as treatment options for stroke survivors with chronic UE deficits, the degree of improvement in the primary endpoints does not qualify as a clinically significant change according to Van der Lee et al.,[13] who suggest 10% improvement on an absolute scale. Inspection of the data reveals that both groups had non-responders, defined by those who maintained or decreased their scores on variables. In fact, the treatment effect for our primary variables ranges from 11 to -5 on the FM and an improved timing of -23.1 to 9.7 sec for the WT illustrating a wide range of response. One explanation of the small treatment effects might be low training intensity. Both groups received training for a total of 360 minutes (about 1 hour per week) which is less than other targeted UE interventions in chronic stroke. Recall that BATRAC intensity

was not increased by progressing speed or movement resistance. A second, related, explanation might be the large severity deficit range enrolled in this trial. Although severity level was not a significant predictor for most variables in this trial, one can argue that participants at both ends of the spectrum might benefit from a more intensive training regimen to overcome floor or ceiling effects. A third explanation could be trainer-related. Although trainers were spread evenly across both groups and a post-hoc analysis revealed no trainer effect for responders/non-responders, it is plausible that, at least compared to a previous BATRAC study, they were less aggressive in progressively extending the excursion of the paretic arm during BATRAC training. This could theoretically account for both the lack of a between group advantage for BATRAC and the small effect size for the BATRAC group. In currently running studies we are exploring a more targeted population range and a more intense, progressive form of BATRAC as well as combining BATRAC with other complementary treatments. We also are exploring whether any subject characteristics predict who will best benefit from BATRAC and/or DMTE. Nevertheless, despite the smaller than anticipated motor function changes and the lack of superiority of BATRAC, this trial has demonstrated differences between the treatments at the underlying neural mechanism level

The comparable outcomes of improving motor function, despite the different brain activation responses, suggest that BATRAC and DMTE may produce their improvements through different mechanisms. We previously showed that participants who improve arm function after BATRAC show bihemispheric, mainly contralesional, activation of premotor cortex by fMRI, while those that do not improve lack this activation [30]. The present data confirm this finding by showing that activation increases in the contralesional superior frontal gyrus after BATRAC but not DTME and that this increase is associated with improved in arm function. The 'superior frontal gyrus' ROI is the same region identified in our previous analysis as well as by other investigators [49-54]as a region modified during recovery of UE function. In contrast to BATRAC, DMTE is associated with smaller increments in brain activation which are distributed among different brain regions (except in the ipsilesional premotor cortex, where activation

increase correlates with DMTE-related WT improvement). It also must be taken into consideration that DMTE-related changes in brain activation in this study did not meet strict statistical criteria applying to multiple comparisons. Taken together, these findings indicate that despite similar improvements in arm function, BATRAC and DTME operate through different brain mechanisms or that DTME makes more use of adaptations that are outside the brain or not measured by fMRI. These differences may be due to the different circuitry utilized in bilateral and unilateral arm movements as described earlier.

Supramarginal gyrus and anterior cingulate cortex are other brain regions where changes in brain activation correlated with improved arm function after BATRAC. The supramarginal gyrus may be involved in attention [55], handwriting movements (left hemisphere region in right-handed participants) [56] and spatial perception [57] and is shown to change activation during recovery of function [51, 58]. Activation changes in this region during BATRAC may be related to the participant paying more attention while moving the paretic arm, or reflect improvements in spatial perception of the paretic arm after BATRAC therapy. Both mechanisms could improve arm function on WMFT and FM tests. The anterior cingulate cortex (ACC) is involved, among various other tasks, in error-based movement learning [59]. Activation in this region after BATRAC may reflect motor learning mechanisms that are recruited by the therapy.

Other neurorehabilitative therapies based on motor learning strategies, are associated with brain activation. Juenger et al., [60] showed that CIMT leads to increases and shifts of activation in frontal and motor cortices, mainly in the lesioned and to a lesser extent in the non-affected hemisphere in chronic stroke survivors, [61] that parallel alterations in brain structure [54]. A recent review concluded that no single pattern of CNS change is observed during recovery; rather, the pattern of neuroplasticity seems to depend on the training intervention and the subject's deficits due to the initial lesion[62]. Our findings support the differential activation change owing to training program.

Conclusion

Six weeks of BATRAC or DMTE improve global arm impairment and function comparably in chronic stroke survivors. Each treatment produced common and different improvements in UE function that were sustained for at least 4 months. The improvements after BATRAC appear mediated, at least in part, by cortical remodeling centered in the ipsilesional precentral gyrus and the contralesional superior frontal gyrus (premotor cortex), whereas DMTE seems to affect other neuroplastic processes. A BATRAC intervention of increased intensity and duration, coupled with DMTE and other UE interventions may be necessary to capitalize on this neuroplasticity to maximize improvements in UE function.

Table 1. Baseline Characteristics for the Treatment Groups

	Entire Cohort			fMRI Subcohort		
	BATRAC (n = 42)	**DMTE (n= 50)**	**P value**	**BATRAC (n=17)**	**DMTE (n=21)**	**p-value**
Age, yr	59.8 (9.9)	57.7(12.5)	0.37	61.2 (13.8)	54.8 (13.1)	0.15
Women, #, (%)	16 (38)	26 (62)		10 (59)	10 (48)	
Men, #, (%)	26 (52)	24 (48)	0.37‡	7 (41)	11 (52)	0.49‡
Time since stroke*, yr	4.5 (4.1)	4.1 (5.2)	0.68	3.9 (2.7)	3.3 (2.1)	0.62
Stroke Location, # (%)						
Brainstem	3 (50)	3 (50)		1 (6)	2 (10)	
Cerebellar	0 (0)	2 (100)		0 (0)	0 (0)	
Cortex	19 (49)	20 (51)		9 (53)	9 (43)	
Multiple	3 (100)	0 (0)		0 (0)	0 (0)	
Subcortical	7 (37)	12 (62)		7 (41)	10 (48)	
Unknown or missing, # (%)	10 (56)	14 (44)	0.12‡	0 (0)	0 (0)	0.89‡
Right hand dominant, #. (%)	36 (48)	39 (52)		15 (88)	13 (62)	
Left hand dominant, No. (%)	6 (35)	11 (65)	0.42†	2 (40)	8 (38)	0.14†
Non-Motor Dominant Stroke, No. (%) paretic arm is non-dominant	24 (57)	26 (60)		10 (59)	12 (57)	
Motor Dominant Stroke, No. (%)	18 (43)	24 (40)	0.81‡	7 (41)	9 (43)	0.92‡
Right-sided Stroke, No. (%)	23 (48)	25 (52)		10 (59)	13 (62)	
Left-sided Stroke, No. (%)	18 (42)	25 (58)	0.53‡	7 (41)	8 (38)	0.85‡
Bilateral Stroke, No. (%)	1 (100)	0 (0)				
Fugl-Meyer score (max 66)	32.3 (14.1)	31.0 (14.8)	0.67	32.0 (12.5)	27.1 (11.6)	0.22
Wolf Time score (in secs)	54.0 (35.6)	54.1 (38.5)	0.99	55.4 (38.5)	66.0 (35.7)	0.39
Wolf Function score (max 4)	1.8 (0.6)	1.9 (0.7)	0.41	1.74 (0.55)	1.63 (0.62)	0.57
Wolf Weight score (in lbs)	2.6 (2.8)	2.5 (3.1)	0.71	2.5 (2.6)	1.8 (3.3)	0.50
Stroke Impact Scale (max is 59)	546 (98)	559 (104)	0.54	538 (73)	556 (81)	0.48

Data are mean (SD) except where otherwise noted. † Fisher's exact test‡ Chi-square

Max. scores for Wolf Time and Wolf Weight are unknown but approximately 1 second and 40 lbs respectively. Wolf Time and Stroke Impact Scale have low best scores.

Table 2. Significant motor function changes in primary and secondary measures

		BATRAC				DMTE			
Measure±SE	n	Baseline*	Change*	Within Grp p	n	Baseline*	Change*	Within Grp p	Between Grp p
Fugl-Meyer (max 66)	42	32.3±2.2	1.1±0.5	**0.03**	50	31.0±2.1	1.9±0.4	**0.00**	0.22
Wolf Motor									
Time (min 120s)	42	54.0±5.5	-2.6±0.8	**0.00**	50	54.1±5.5	-1.6±0.7	**0.04**	0.40
Weight (max 10lbs)	40	2.6+0.4	0.4+0.2	**0.00**	47	2.5+0.4	0.2+0.1	0.44	0.11
Function (max 4)	42	1.8±0.1	0.0±0.0	**0.03**	50	1.9±0.1	0.1±0.0	**0.00**	0.58
SIS									
Emotion	37	82.1±2.3	2.5±1.8	0.24	42	82.9±2.4	3.6±1.7	**0.01**	0.30
Hand	37	24.6±4.9	6.5±3.0	**0.03**	42	27.7±5.0	6.2±2.5	**0.03**	0.91
Strength	37	48.3±3.5	7.0±3.1	**0.01**	42	52.2±3.2	3.7±1.9	0.10	0.37
Total Score	37	549±17	12±6.1	0.14	42	578±15	26±8.9	0.00	0.19
Isokinetic Strgth kg/s									
Non-paretic									
Elbow Ext	41	16.6±0.8	1.8±0.8	**0.03**	46	16.1±0.7	0.7±0.8	0.33	0.35
Elbow Flex	41	33.3±2.3	1.8±1.1	0.09	46	36.9±2.7	-1.5±0.8	0.13	**0.03**
Paretic									
Elbow Ext	41	13.9±1.2	1.6±0.8	**0.01**	46	13.5±1.4	0.8±0.5	0.33	0.24
Isometric Strgth kg									
Non-Paretic									
Should Ext	42	17.6±0.9	1.4±0.4	**0.00**	50	18.1±0.8	0.6±0.4	0.10	0.29
Wrist Ext	42	13.8±0.6	0.9±0.3	**0.01**	50	12.9±0.4	0.5±0.4	0.23	0.25
Wrist Flex	42	11.2±0.6	0.6±0.4	0.09	50	11.4±0.6	-0.6±0.4	0.10	**0.02**
Parctic									
Should Ext	42	8.1±0.7	0.6±0.3	**0.05**	50	7.5±0.9	0.8±0.3	**0.01**	0.64
Wrist Ext	42	3.5±0.6	-0.2±0.2	0.25	50	2.9±0.9	0.7±0.2	**0.00**	**0.00**
Elbow Flex	42	8.4±0.7	0.3±0.3	0.29	50	7.9±0.7	0.9±0.3	**0.01**	0.30

Table 3 Relationship between changes in UE function to brain activation during paretic limb movement

		BATRAC				DTME				
ROI	**side**	**mean increase**	**SE**	**r†**	**p**	**mean increase**	**SE**	**r†**	**p**	**Between group p**
Primary ROI										
precentral gyrus	ipsilesional	1.17	0.20	-0.45	*0.079*	0.48	0.17	-0.23	0.324	**0.011***
	contralesional	1.33	0.27	-0.43	*0.093*	0.83	0.23	-0.45	0.112	0.180
superior frontal gyrus	ipsilesional	1.54	0.17	-0.48	*0.057*	1.08	0.15	-0.12	**0.045**	*0.053*
	contralesional	1.33	0.22	-0.62	**0.010***	0.58	0.19	-0.25	0.290	**0.012***
Secondary ROI										
SMA	ipsilesional	1.34	0.17	-0.12	0.646	0.85	0.15	-0.21	0.365	**0.039**
	contralesional	1.33	0.17	-0.04	0.855	0.89	0.15	-0.13	0.581	*0.066*
ant. cingulate cortex	ipsilesional	1.47	0.27	-0.76	**0.001***	0.70	0.23	-0.28	0.229	**0.036**
	contralesional	1.24	0.24	-0.68	**0.004***	0.59	0.21	-0.09	0.685	*0.052*
supramarginal gyrus	ipsilesional	1.06	0.15	-0.64	**0.007***	0.70	0.13	-0.26	0.260	*0.082*
	contralesional	0.96	0.12	-0.69	**0.003***	0.77	0.10	-0.45	**0.044**	0.239
cerebellum, ant. lobe	ipsilesional	1.17	0.18	-0.17	0.501	1.09	0.16	-0.14	0.531	0.707
	contralesional	1.03	0.17	-0.17	0.537	0.59	0.15	-0.30	0.188	*0.060*
cerebellum, post. lobe	ipsilesional	1.68	0.32	-0.10	0.709	2.08	0.28	-0.26	0.273	0.349
	contralesional	1.55	0.22	-0.39	0.142	1.64	0.19	-0.42	*0.059*	0.767
postcentral	ipsilesional	0.91	0.13	-0.24	0.376	0.50	0.11	-0.55	**0.012**	**0.023**
	contralesional	0.88	0.13	-0.44	*0.088*	0.59	0.11	-0.51	**0.022**	*0.095*

† Pearson's r; Bold = p <..05; Italics = p >.05 <.1; * = remained significant after Bonferroni corrections

Figure 1

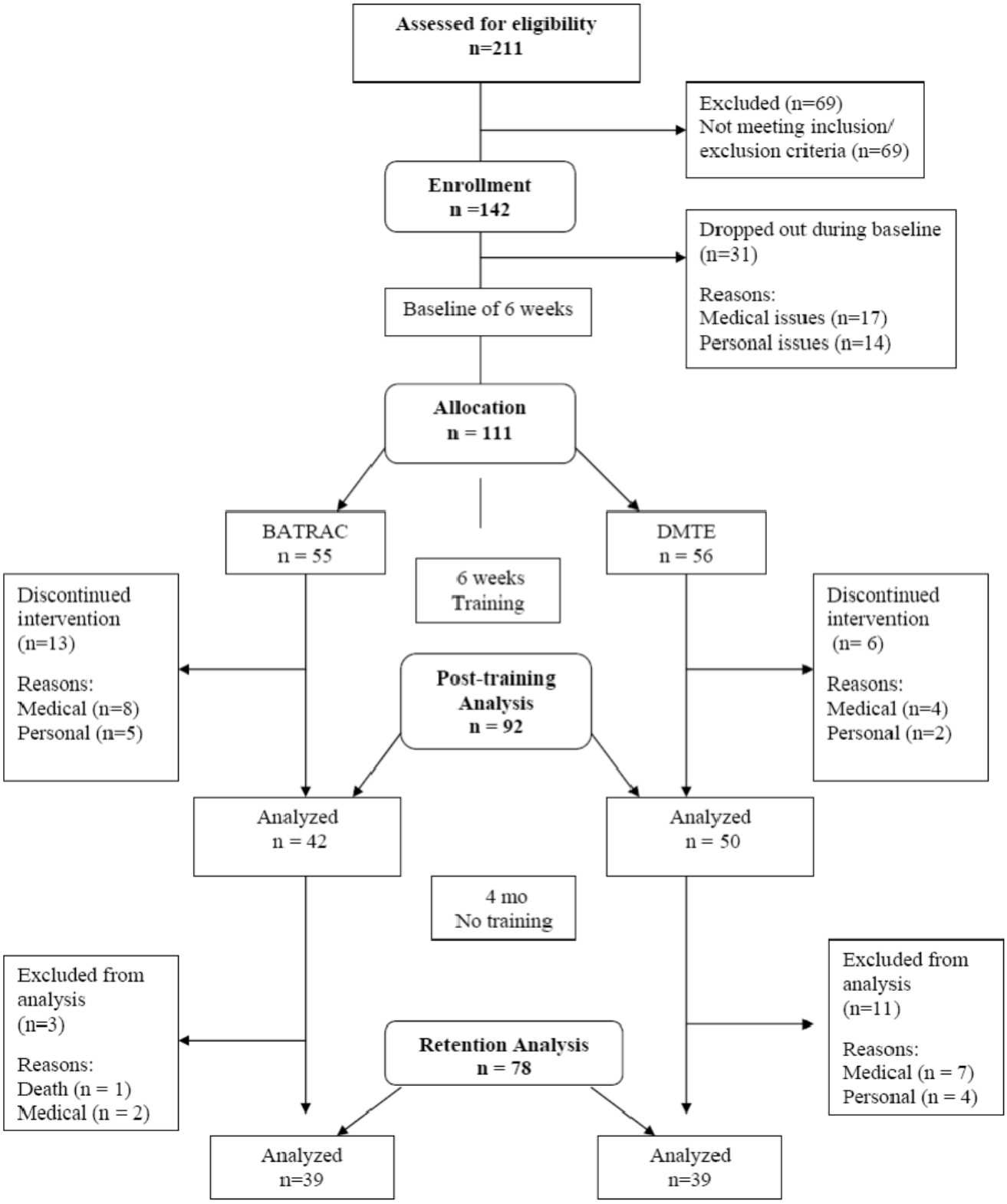
Assessed for eligibility
n=211
Excluded (n=69)
Not meeting inclusion/
exclusion criteria (n=69)
Enrollment
n =142
Dropped out during baseline
(n=31)
Reasons:
Medical issues (n=17)
Personal issues (n=14)
Baseline of 6 weeks
Allocation
n = 111
BATRAC
n = 55
DMTE
n = 56
6 weeks
Training
Discontinued
intervention
(n=13)
Reasons:
Medical (n=8)
Personal (n=5)
Discontinued
intervention
(n= 6)
Reasons:
Medical (n=4)
Personal (n=2)
Post-training
Analysis
n = 92
Analyzed
n = 42
Analyzed
n = 50
4 mo
No training
Excluded from
analysis
(n=3)
Reasons:
Death (n = 1)
Medical (n = 2)
Excluded from
analysis
(n=11)
Reasons:
Medical (n = 7)
Personal (n = 4)
Retention Analysis
n = 78
Analyzed
n=39
Analyzed
n=39

Figure 2.

Two primary regions of interest, precentral gyrus (blue) and superior frontal gyrus (green), are presented superimposed onto a T1-weighted scan of an exemplary subject. These ROI were pre-specified based on prior studies and defined using the AAL atlas.

Figure 3.

The increase in activation in the contralesional superior frontal gyrus (ipsilateral to the moving paretic limb) correlated with faster performance in the WMFT (time post-training – time pre-training) in BATRAC-trained subjects ($r=-0.62$, $p=0.010$). No such correlation was found in the DMTE group.

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